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Oral contraceptives and primary liver cancer among young women

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The association of oral contraceptive use with liver cancer was examined in a study of 76 deaths from primary liver cancer, 22 deaths from cancer of the intrahepatic bile ducts, and 629 controls among women aged 25 to 49 years. The subjects in the study are from the 1986 National Mortality Followback Survey, which included a questionnaire sent or administered to the next-of-kin of almost 20,000 deceased individuals in the United States. Information on a number of lifestyle factors was collected, including questions on oral contraceptive use. Increased risks of primary liver cancer were found for ever-users (odds ratio [OR] = 1.6, 95 percent confidence interval [CI] = 0.9-2.6), and for long-term (≥ 10 years) users (OR = 2.0, CI = 0.8-4.8) of oral contraceptives. When the analysis was restricted to subjects whose spouse or parent was the respondent, more pronounced risks were seen for ever-users (OR = 2.7, CI = 1.4-5.3) and long-term users (OR = 4.8, CI = 1.7-14.0). No clear excess risk was found for cancer of the intrahepatic bile ducts. This study, the largest to date, adds to the number of investigations demonstrating an increased risk of primary liver cancer with use, particularly long-term use, of oral contraceptives.

Key words: Case-control study, liver cancer, oral contraceptive use, United States.

Introduction

Laboratory, clinical, and epidemiologic studies have linked estrogen use with liver neoplasms. In rats, synthetic estrogens have induced liver tumors.[1] In humans, case reports have linked oral contraceptive (OC) use with hepatic cell adenoma,[2] focal nodular hyperplasia of the liver,[3] and hepatocellular carcinoma.[4,5] Further, six case-control studies from Western countries have reported an increased risk of primary liver cancer (PLC), especially hepatocellular carcinoma, among long-term (> 5 years) users of OCs.[6-11] Because PLC is relatively rare in developed countries, these studies were limited in size, ranging from 12 to 26 patients. A recent review of epidemiologic data on hepatocellular carcinoma estimated overall relative risks (RR) of 2.6 (95 percent confidence interval [CI] = 1.3-5.1) for ever-users and 9.6 (CI = 4.0-22.8) for long-term users in low-incidence countries.[12] In developing countries with a high incidence of PLC, two studies revealed no association with oral contraceptives.[13,14]

A 1987 National Health Interview Survey of 12,747 women aged 18-68 showed that about 80 percent of the women born after 1945 and 50 percent born prior to 1945 have used OCs at some time.[15] Due to the high prevalence of OC use, its role in PLC etiology needs clarification, especially with prolonged exposure. We had an opportunity to address this issue in a case-control study, the largest to date, of PLC among women in the United States between the ages of 25 and 49 identified in a nationwide mortality survey. Since PLC is rare in women younger than age 25 and use of OCs is

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relatively low in women born prior to 1935, study subjects were restricted to those 25 to 49 years of age.

Methods

National Mortality Followback Survey (NMFS)

Study subjects were selected from the 1986 National Mortality Followback Survey (NMFS) of 18,733 decedents, conducted by the National Center for Health Statistics (NCHS). The development and design of the 1986 survey are described in detail elsewhere.[16] Briefly, the 1986 NMFS was a representative sample of US adult deaths (> 25 years), excluding Oregon because of the state's respondent consent requirements. The 1986 Current Mortality Sample (CMS), a 10 percent systematic sample of death certificates sent by state vital statistics offices to NCHS approximately three months after death, was used to select samples for the NMFS study.

Death certificates were obtained for all decedents in the NMFS study, and questionnaires were sent to next-of-kin of the decedents to obtain information on the following: use of oral contraceptives, cigarettes, and alcohol; food consumption patterns; and health service-related questions. The response rate for the informant questionnaire was 89 percent.

Cases

Because PLC is relatively rare in the US, especially at young ages, only 17 deaths attributed to liver cancer (International Classification of Diseases, Ninth Revision [ICD9] code 155) among women aged 25 to 49 were available from the CMS for the 1986 NMFS study. To obtain more cases for our investigation, all US women, except those from Oregon, who died of liver cancer (ICD9 code 155) in 1985 between the ages of 25 and 49 ($n = 186$) were added to the study. (The 1986 NMFS questionnaire and identical procedures for contacting next-of-kin were employed to obtain information for these 186 cases.) Of the total 203 liver cancer deaths, we excluded 52 cases with liver cancer not specified as primary (ICD9 code 155.2) and four cases with chronic liver disease mentioned as other significant conditions on the death certificates, leaving 147 subjects eligible for study. Of these, 29 cases with a history of liver cirrhosis reported by the next-of-kin and 20 cases who had no respondents were not included, leaving 98 for final analysis; 76 deaths were due to PLC (ICD9 code 155.0), and 22 to cancer of the intrahepatic bile ducts (ICD9 code 155.1).

Controls

Women from the 1986 NMFS study who died between the ages of 25 and 49 of causes other than liver cancer (ICD9 code 155) and whose next-of-kin responded to the informant questionnaire were eligible to be con-

Table 1. Percent[a] distribution of selected characteristics among cases and controls

Selected characteristics	Primary liver cancer[b]		Intrahepatic bile duct cancer[c]		Controls	
	No.	%	No.	%	No.	%
Total	76	100.0	22	100.0	629	100.0
Age at death						
25-29	16	21.0[d]	0	0.0[c]	148	23.5
30-34	8	10.5	4	18.2	131	20.8
35-39	21	27.6	4	18.2	131	20.8
40-44	10	13.2	5	22.7	146	23.2
45-49	21	27.6	9	40.9	73	11.6
Race						
White	60	78.9[d]	17	77.3	449	71.4
Black	10	13.2	3	13.6	145	23.0
American Indian	0	0.0	1	4.5	23	3.7
Other	6	7.9	1	4.5	12	1.9
Marital status at time of death						
Never married	8	10.5[d]	1	4.5[c]	141	22.9
Divorced	9	11.8	4	18.2	120	19.5
Separated	2	2.6	0	0.0	52	8.4
Widowed	4	5.3	0	0.0	22	3.6
Married	53	69.7	17	77.3	281	45.6
Type of respondent						
Spouse	42	56.0[d]	11	50.0[c]	206	32.8
Parent	11	14.7	2	9.1	225	35.8
Child	9	12.0	5	22.7	51	8.1
Sibling	5	6.7	1	4.6	70	11.1
Other	8	10.7	3	13.6	77	12.2
Years of education						
< 5	4	5.3	1	4.8	22	3.6
5-8	7	9.2	3	14.3	43	7.1
9-12	43	56.6	12	57.1	359	59.1
> 12	22	28.9	5	23.8	183	30.1
Total annual family income						
< $11,000	18	28.6	4	23.5	183	38.6
$11,000-$24,999	18	28.6	4	23.5	141	29.7
≥ $25,000	27	42.9	9	52.9	150	31.6
Cigarette smoking						
Nonsmoker	38	50.0	7	33.3	264	43.9
Former smoker	10	13.2	6	28.6	103	17.1
Current smoker	28	36.8	8	38.1	235	39.0
Alcohol use						
Nonuser	23	30.3	5	23.8	150	24.6
User	53	69.7	16	76.2	460	75.4

[a] Missing data not included in percent calculation; percentage may not add to 100.0 due to rounding.
[b] ICD9 code = 155.0.
[c] ICD9 code = 155.1.
[d] $P < 0.05$, comparison between primary liver cancer cases and controls.
[c] $P < 0.05$, comparison between intrahepatic bile duct cancer cases and controls.

trols ($n = 1,372$). Of these, 91 women with chronic liver disease mentioned as an underlying cause of death or as other significant conditions on the death certificate, including viral hepatitis (ICD9 code 070, $n = 3$), necrosis of the liver (ICD9 code 570, $n = 1$), liver cirrhosis (ICD9 code 571, $n = 54$), liver abscess (ICD9 code 572, $n = 30$), and other disorders of the liver (ICD9 code 573, $n = 3$), were excluded. In addition, another 47 women with a history of liver cirrhosis reported by the next-of-kin were dropped. A total of 605 women with causes of death thought to be associated with oral contraceptive use also were excluded (comprising 18 broad diagnostic categories: 18 percent died of breast cancer; 53 percent of heart disease; and eight percent of cerebrovascular disease), leaving 629 controls for the final analysis (comprising 31 broad diagnostic categories: 43 percent died of injury or poisoning; 26 percent of cancer; and nine percent of respiratory diseases). A complete list of diagnostic categories for excluded and included controls is available upon request.

Statistical analysis

Odds ratios (OR) for hepatocellular carcinoma for ever- and long-term users, relative to women who had never used oral contraceptives, were estimated using multiple logistic regression analysis simultaneously controlling for the following potential confounding factors: age at death (five-year intervals); race (White, Black, other); annual family income (< $11,000, $11,000-$24,999, ≥ $25,000); cigarette smoking (ever/never); and alcohol use (ever/never).[17]

Results

Selected characteristics for cases dying of PLC and of intrahepatic bile duct cancer and for their controls are shown in Table 1. Compared to controls, cases were older, were more likely to be White and married, to have a spouse or parent as respondent, and to have a higher annual family income. Within each marital category, there was no difference in respondent status (spouse/parents *cf* others) between cases and controls.

Table 2 shows that among subjects with a spouse or parent as respondent, risks of PLC were significantly elevated for ever-users of OCs and among those who used OCs for more than five years. The risk was non-significantly below unity among subjects with other surrogate respondents (children, siblings, or friends), although information on OC use was missing (14 percent of cases and 20 percent of controls) for many of these respondents (data not shown). Use of OCs was associated with increased risk regardless of age at first use, although ORs were higher for those using OCs before age 25. When Asian cases ($n = 4$) and controls ($n = 10$), presumably having a higher prevalence of hepatitis-B infection, were excluded from the analysis,

Table 2. Odds ratios[a] and 95% confidence intervals (CI) for primary liver cancer associated with oral contraceptive use, by type of respondent

Oral contraceptive status	Spouse or parent respondent[d]				All subjects[c]			
	Cases	Controls	OR	CI	Cases	Controls	OR	CI
Total	52	391			72	549		
Use								
Nonuser	17	211	1.0		33	306	1.0	
Ever-user	35	180	2.7	1.4-5.3	39	243	1.6	0.9-2.6
Years of use[d]								
< 5 years	15	93	2.1[e]	0.9-4.6	16	121	1.2[f]	0.6-2.4
5-9 years	13	48	3.9	1.6-9.6	13	61	2.0	1.0-4.4
≥ 10 years	7	26	4.8	1.7-14.0	8	41	2.0	0.8-4.8
Age at first use[c]								
13-19	8	51	2.9	1.1-7.6	8	75	1.2	0.5-2.7
20-24	13	72	3.0	1.3-7.2	13	87	1.4	0.7-3.0
≥ 25	10	37	2.1	0.8-5.6	11	51	1.6	0.7-3.5

[a] Adjusted for age at death, race, annual family income, use of alcohol, and smoking; nonuser is the reference category.
[b] Does not include one case, 40 controls with missing data.
[c] Does not include four cases, 80 controls with missing data.
[d] Does not include users with missing data.
[e] Test for trend, $P < 0.001$.
[f] Test for trend, $P = 0.07$.

Table 3. Odds ratios[a] for primary liver cancer associated with age at first use and duration of oral contraceptive use among subjects with a spouse or parent respondent only

Duration of use	Age at first use											
	13-19				20-24				≥25			
	Cases	Controls	OR	CI	Cases	Controls	OR	CI	Cases	Controls	OR	CI
Nonuser	17	211	1.0		17	211	1.0		17	211	1.0	
User[b]												
< 5 years	3	21	1.6	0.4-6.9	5	39	1.9	0.6-6.1	3	28	0.9	0.2-3.7
5-9 years	3	18	2.7	0.6-11.7	4	21	3.2	0.8-12.4	6	7	5.6	1.3-24.3
≥ 10 years	2	10	7.2	1.1-45.3	4	11	5.6	1.4-23.3	1	2	6.6	0.2-206.4
P for trend			*P* = 0.04				*P* = 0.01				*P* = 0.06	

[a] Adjusted for age at death, race, annual family income, use of alcohol, and smoking; nonuser is the reference category.
[b] Did not include subjects with unknown age at first use.

higher risk estimates were seen for ever-use (OR = 2.8, CI = 1.4-5.5) and long-term (≥ 10 years) use (OR = 5.2, CI = 1.7-15.4).

Age at first use and duration of use of oral contraceptives in relation to PLC risk were examined together in Table 3. For each category of age at first use, risks rose with increasing duration of use.

No information was available on type and dosage of oral contraceptive use and time since last use. Although we were unable to evaluate fully the effect of current use, when age at first use, age at death, and duration of use were examined together, there was some suggestion that recency of use may be an important factor (data not shown).

Use of OCs increased the risk of PLC among Blacks and Whites, regardless of education, income levels, parity or geographic regions. Risk of PLC did not change materially when causes of death speculated as being possibly related to OC use were excluded from the analysis. These included malignant melanoma ($n = 13$), and cancers of the colon ($n = 14$) and thyroid ($n = 1$).

The risk of intrahepatic bile duct cancer in relation to OC use was analyzed (Table 4). No clear association was found, with the only increased risk (OR = 3.3, CI = 0.7-15.9) among women using OCs for 10 or more years.

Table 4. Odds ratios[a] and 95% confidence intervals (CI) for cancer of the intrahepatic bile ducts associated with oral contraceptive use among subjects with a spouse or parent respondent only

Oral contraceptive status	Cases	Controls[b]	OR	CI
Use				
Nonuser	7	211	1.0	
Ever-user	6	180	0.8	0.3-2.7
Years of use				
< 5 years	2	93	0.5	0.1-2.7
5-9 years	1	48	0.6	0.1-5.4
≥ 10 years	3	26	3.3	0.7-15.9
Age at first use				
13-19 years	2	51	1.3	0.2-7.6
20-24 years	0	72	—	—
≥ 25 years	4	37	1.8	0.4-7.4

[a] Adjusted for age at death, race, annual family income, use of alcohol, and smoking; nonuser is the reference category.
[b] Does not include 40 controls with missing data.

Discussion

Consistent with six previous case-control studies,[6-11] our findings indicate that the use of OCs enhances the risk of developing PLC among young women in populations with a low prevalence of hepatitis-B virus (HBV) infection. We found that the risk of PLC rose with duration of OC use, although age at first use was not a key factor. In contrast, OC use did not appear to be related to intrahepatic bile duct cancer, although the number of cases was small.

Chronic HBV infection is the major risk factor for liver cancer in developing countries and may contribute to some cases in the US. Since the prevalence of HBV infection is relatively low in Western countries (about three percent in the US),[18] previous studies usually excluded women with a history of HBV infection. No information on HBV infection was available, so we excluded women with HBV-related conditions on their death certificates. In addition, exclusion from the analysis of Asian cases and controls, who may have a higher prevalence of HBV infection, resulted in a stronger association with oral contraceptives.

The relationship of birth control pills to PLC in HBV-endemic areas is not clear, since the prevalence of OC use is relatively low, with few long-term users, and the risk associated with HBV infection is high. In these areas, the power to detect small to moderate increases in risk from OCs has been low.[13,14] Further studies are needed, for if OCs interact with HBV infection to enhance risk of PLC, their use in developing countries would have important public health implications.

Although accurate recall of OC use is difficult for many women, it has been shown that ever/never use, current use, and duration of use are reliably remembered.[19] Husbands also have been found to report relatively accurately on their wives' current or past use of birth control pills, although often unable to indicate the brand or give an estimate of the duration of use.[20] Due to anticipated recall problems with surrogate interviews, the NMFS questionnaire sought only minimal information on OCs. Nevertheless, some nondifferential misclassification of ever-use, duration of use, and age at starting OC use is likely and could decrease the association of OCs with liver cancer. Differential reporting of OC use between cases and controls is possible if the surrogate respondents of cases were sensitized to the OC hypothesis. However, we could not assess this bias in the study. Such bias, if it exists, should be minimal, since controls were also deceased. Although we were unable to evaluate the effect of current use directly, our data suggest that recency of use may be important. It will be of interest in future studies to evaluate the risks of current *cf* past users of OCs and the risk after cessation of use.

In this study, the excess risk of PLC associated with OCs was confined to subjects with a spouse or parent as the surrogate respondent. Considering the age of the study subjects, spouses and parents are likely to provide more accurate information on OC use than other types of respondents. The prevalence of reported use was 39 percent for all controls and 42 percent for controls with a spouse or parent respondent. Furthermore, the percentages with missing information on use, including age at which OC use started and duration of use, were considerably lower for spouses and parents than for other respondents (14 percent *cf* 24 percent).

Since liver is a common site of metastasis, some cases of secondary liver cancer are likely to have been misclassified and reported as PLC on death certificates. One study examined the hospital records of 6,734 subjects with liver cancer (ICD9 code 155) mentioned as an underlying cause of death on their death certificates, and of another 2,977 subjects with PLC (ICD9 code 155.0) as an underlying cause.[21] It found that 57 percent of the reported liver cancers and 83 percent of the PLCs were confirmed by a hospital diagnosis. Reliance on death certificates for diagnosis of PLC is not optimal. Thus, to minimize the effect of misclassification of liver cancer, we analyzed only cases specifically identified as PLC and intrahepatic bile duct cancer. Any remaining misclassification would probably have lowered our estimate of risk from the true value.

Possible confounding by smoking and drinking should be considered for several reasons. Prolonged and excessive use of alcohol is an established risk factor for PLC, while cigarette smoking has been suggested by some studies as a contributing factor in low-incidence areas.[22-24] Users of OCs are more likely to be smokers than nonusers.[25] Also, intake of alcohol and tobacco use are related to mortality even after exclusion of smoking- and alcohol-related causes of death.[26,27] In our study, controlling for tobacco and alcohol use (either frequency of use or amount of consumption) had no influence on estimates of risk.

The mechanism of hepatocarcinogenesis in OC users is not entirely clear, although the estrogenic agents present in OCs are known to induce hepatic tumors in laboratory animals.[28] In humans, there is evidence that OC-related adenomas of the liver may progress to carcinoma[29] and regress following cessation,[30,31] and that estradiol receptors are present in normal liver tissue and in hepatocellular tumors.[32,33]

Although combination OCs are considered a human carcinogen by the International Agency for Research on Cancer,[34] the causal relationship with hepatocellular carcinoma is often overlooked, perhaps due to its low incidence among young women in developed countries, and to the small number of reported cases in earlier studies. More often cited is the increased risk suggested in some (but not all) studies of breast and cervix cancers, and the decreased risk of ovarian and endometrial cancers, from use of combination OCs.

Since OC use increases the risk of hepatocellular carcinoma, an increase in liver cancer incidence among young women might be expected in the 20 years since OCs became commercially available in the 1960s. Such an increase in liver cancer mortality has been reported in England,[35] while no increase in incidence has been seen among young women in the US during 1970-88.[36] Since the excess risks appear to be most prominent among OC users of five to 10 years or more, perhaps not enough time has elapsed yet for an effect to appear in the US statistics.

In summary, despite limited information on subjects with PLC and possible misclassification of OC use in our study, we found an almost fivefold risk of PLC among long-term OC users. The findings are consistent with the excess risks of hepatocellular carcinoma previously reported in smaller case-control studies carried out in Western countries with a generally low inci-

dence of this cancer. It is time to consider a large-scale incident case-control study, with a serologic component for evaluation of hepatitis B and C infection status, to determine the risk of PLC among current and long-term OC users with and without evidence of hepatitis infection.

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